

## REMARKS

### Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, and 4-6 are rejected under 35 U.S.C. § 103(a) as unpatentable over *Catterall et al.* (“*Catterall*”) in view of *Connolly et al.* (“*Connolly*”). Claims 1-6 are also rejected under 35 U.S.C. § 103(a) as unpatentable over *Catterall* and *Connolly* in view of *Tung et al.* (“*Tung*”).

Only one independent claim remains pending in the present application. Independent Claim 1 recites a “method of screening a plurality of drug candidate compounds against a target ion channel comprising . . . modulating a transmembrane potential of host cells in said plurality of sample wells with a repetitive application of electric fields applied with extracellular electrodes so as to set said transmembrane potential to a level corresponding to a pre-selected voltage dependent state of said target ion channel.”

This is illustrated, for example, in Figures 10-13 in the specification of the instant application. As illustrated in these Figures, the transmembrane potentials are set to a pre-selected level depending upon the applied voltage parameters. Figure 13 illustrates how variation in pulse parameters produces variation in the set transmembrane potentials. Thus, depending on the particular applied electric field, the transmembrane potential may be set “to a level corresponding to a pre-selected voltage dependent state of [a] target ion channel” using extracellular electrodes with the principles and methods described in the specification.

Claim 1 is not obvious in light of *Catterall* and *Connolly* or in light of *Catterall*, *Connolly* and *Tung*. *Catterall* specifically teaches breaking through the cell membrane and inserting an electrode into a cell to directly manipulate the membrane potential. See *Catterall* at col. 3 lines 20-25. *Connolly* describes an extracellular stimulation of cardiac cells “to initiate beating,” see *Connolly* at page 232. One of skill in the art would not be motivated to select the electrodes of *Connolly* for use in the system of *Catterall*. The intracellular voltage recordings when using the extracellular electrodes of *Connolly* show repeated spiked signals less than a second in duration. The applied electric field initiates a complex cellular response and does not set the transmembrane potential to any selected level, and certainly does not teach setting a transmembrane potential to a level that corresponds to a pre-selected voltage dependent state of a target ion channel. See *Connolly* at page 230, Figure 5. Setting a transmembrane potential to a

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pre-selected voltage state was not the object of *Connolly*, and one of ordinary skill in the art would not select the extracellular electrodes taught by *Connolly* for setting the transmembrane potential of a cell as claimed.

Similarly, *Tung* does not teach or suggest “set[ting] a transmembrane potential to a level corresponding to a pre-selected voltage dependent state of [a] target ion channel” with an externally applied electric field. The theoretical models of *Tung* show complex and highly varying transmembrane potentials. See e.g. *Tung* at page 376, Figure 3. Thus, *Tung* does not teach or suggest “set[ting] a transmembrane potential” to a level corresponding to a pre-selected voltage dependent state of a target ion channel, and one of skill in the art would not be motivated to use the external electric fields of the *Tung* models to set transmembrane potentials as claimed. *Tung* determines that “electrical stimulation of cardiac cells by imposed extracellular electric fields results in a transmembrane potential which is highly nonuniform.” See *Tung* at Abstract (emphasis added). Thus, *Tung*, like *Connolly*, does not provide one of ordinary skill in the art any reason to abandon a known and consistently used patch clamping method. Thus, the combinations of *Catterall* with *Connolly* or *Catterall* with *Connolly* and *Tung* are not obvious.

The applicant respectfully submits that in rejecting Claim 1, the Examiner simply determined obviousness based on hindsight combination of components selectively culled from the prior art. One of ordinary skill in the art would not have thought that extracellular stimulation could set transmembrane potentials at desired levels as can be done with a patch clamping method. Accordingly, one of ordinary skill in the art would not have been motivated to selectively combine the teachings of *Catterall* with *Connolly* or the teachings of *Catterall*, *Connolly* and *Tung* as argued by the Examiner. Thus, Applicants respectfully request that the Examiner’s rejection of Claim 1 based on *Catterall*, *Connolly*, and *Tung* be withdrawn.

Claims 1, 2, and 4-7 are also rejected under 35 U.S.C. § 103(a) as unpatentable over *Catterall* and *Connolly* in view of *Tsien et al.* or *Denyer et al.* The Examiner states that “*Tsien et al.* and *Denyer et al.* are combined with *Catterall et al.* and *Connolly et al.* only to teach the use of voltage sensors.”

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As noted above, Claim 1 is not obvious in light of *Catterall* and *Connolly*. Neither *Tsien* nor *Denyer* remedies that deficiency. Indeed, the Examiner cites *Tsien* and *Denyer* "only to teach the use of voltage sensors." While *Tsien* stimulates a transmembrane electrical potential with chemical stimulation and *Denyer* discloses ion channel assays with radio tracers, neither *Tsien* nor *Denyer* renders obvious a combination of *Catterall* and the extracellular stimulation of *Connolly*. Thus, Applicants respectfully request that the Examiner's rejection of Claim 1 on this basis be withdrawn.

Claims 2-7 are dependent on Claim 1, and it is respectfully submitted that these claims are also patentable for at least the same reasons as set forth above with regard to Claim 1.

### CONCLUSION

The Applicants have endeavored to address all of the Examiner's concerns as expressed in the previous Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

If any issues remain that could be resolved by telephone, the Examiner is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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